

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEYS DOCKET NUMBER

Mo-6752/LeA 33,583

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

10/009930

To Be Assigned

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PCT/EP00/04014

04 May 2000 (4.05.00)

PRIORITY DATE CLAIMED

12 May 1999 (12.05.99)

TITLE OF INVENTION
ENDOPARASITICIDAL SYNERGISTIC COMBINATION CONTAINING CYCLIC DEPSIPEPTIDES AND PIPERAZINES

APPLICANT(S) FOR DO/EO/US HARDER, Achim and VON SAMSON-HIMMELSTJERNA, Georg

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☒ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:

Abstract

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO
and International Search Report not prepared by the EPO or JPO. \$1040.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO \$890.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO
but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

CALCULATIONS PTO USE ONLY

\$ 890.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

\$ 0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	10 - 20 =	0	x \$18.00	\$ 0.00
Independent claims	3 - 3 =	0	x \$84.00	\$ 0.00

MULTIPLE DEPENDENT CLAIM(S) (if applicable) + \$280.00

\$ 280.00

TOTAL OF ABOVE CALCULATIONS =

\$ 1,170.00

☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above
are reduced by 1/2.

\$ 0.00

SUBTOTAL =

\$ 1,170.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(f)).

\$ 0.00

TOTAL NATIONAL FEE =

\$ 1,170.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

\$ 40.00

TOTAL FEES ENCLOSED =

\$ 1,210.00

Amount to be
refunded: \$

charged: \$

- a. ☐ A check in the amount of \$ _____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 13-3848 in the amount of \$ 1,210.00 to cover the above fees.
A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
overpayment to Deposit Account No. 13-3848. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card
information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR
1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

SIGNATURE

Godfried R. Akorli

NAME

28,779

REGISTRATION NUMBER



00157

PATENT TRADEMARK OFFICE

10/009930

JC05 Rec'd PCT/PTC 09 NOV 2001

PATENT APPLICATION
Mo-6752
LeA 33,583

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF)
ACHIM HARDER ET AL) PCT/EP00/04014
SERIAL NUMBER: TO BE ASSIGNED)
FILED: HEREWITH)
TITLE: ENDOPARASITICIDAL SYNER-)
GISTIC COMBINATION CON-)
TAINING CYCLIC DEPSIPEPTIDES)
AND PIPERAZINES)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

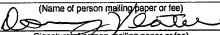
Prior to the examination of the subject application, please make the following amendment.

"Express Mail" mailing label number ET700176797US
Date of Deposit November 9, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

Donna J. Veatch

(Name of person mailing paper or fee)



(Signature of person mailing paper or fee)

IN THE SPECIFICATION:

On page 1 and on the Abstract, delete the title and insert the following:

--ENDOPARASITICIDAL SYNERGISTIC COMBINATION CONTAINING CYCLIC
DEPSIPEPTIDES AND PIPERAZINES--.

A new abstract is enclosed.

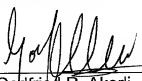
1000000-1000

REMARKS

Applicants have made the amendments to the application so that it better conforms to U.S. practice

Respectfully submitted,

By



Godfried R. Akorli
Attorney for Applicants
Reg. No. 28,779

Bayer Corporation
100 Bayer Road
Pittsburgh, Pennsylvania 15205-9741
(412) 777-8340
FACSIMILE PHONE NUMBER:
(412) 777-8363
s:\ks\6752preamend

VERSION TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 1 and on the Abstract, delete the title and insert the following:

--ENDOPARASITICIDAL SYNERGISTIC COMBINATION CONTAINING CYCLIC
DEPSIPEPTIDES AND PIPERAZINES--.

A new abstract is enclosed.

10000000-10000000

ABSTRACT OF THE DISCLOSURE

The present invention relates to the use of piperazines for increasing the endoparasitocidal action of cyclic depsipeptides, consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms, in endoparasitocidal compositions, such compositions and the use of piperazines and cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms for the production of endoparasitocidal compositions.

Endoparasiticial compositions

The present invention relates to the use of piperazines for increasing the endoparasiticial action of cyclic depsipeptides in endoparasiticial compositions.

Piperazines and their action against endoparasites are generally known. (Mehlhorn et al., Diagnostik und Therapie der Parasitosen des Menschen [Diagnosis and Therapy of Human Parasitoses], 2nd Edition, Gustav Fischer Verlag, (1995), Mehlhorn et al., Diagnostik und Therapie der Parasitosen von Haus-, Nutz- und Heimtieren [Diagnosis and Therapy of Parasitoses of Domestic, Agricultural and Pet Animals], 2nd Edition, Gustav Fischer Verlag, (1993)).

A cyclic depsipeptide PF 1022 and its action against endoparasites is disclosed in EP-OS (German Published Specification) 382 173.

Further cyclic depsipeptides and their endoparasiticial action are the subject of EP-OS (German Published Specification) 0 626 375, EP-OS (German Published Specification) 0 626 376 and WO 93/25543.

The present invention relates to the use of piperazines for increasing the endoparasiticial action of cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and [lacuna] 24 ring atoms.

The present invention further relates to endoparasiticial compositions which contain piperazines together with cyclic depsipeptides consisting of amino acids and hydrocarboxylic acids as ring units and [lacuna] 24 ring atoms.

The present invention further relates to the use of piperazines together with cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and [lacuna] 24 ring atoms for the production of endoparasiticial compositions.

Express Mail mailing label number: **BT00176797US**
Date of Deposit: **November 9, 2001**

I hereby certify that this paper or file is being deposited with the United States Patent and Trademark Office as required by 35 U.S.C. 4201 and 4202, and that the fee of \$1.10 on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

Thomas J. Veatch

(Name of person making deposit)

23



and their optical isomers and racemates.

Preferably, compounds of the formula (I) are employed in which

5 R^1 , R^2 , R^{11} and R^{12} independently of one another represent methyl, ethyl, propyl, isopropyl, n-, s-, t-butyl or phenyl, which is optionally substituted by halogen, C_{1-4} -alkyl, OH, C_{1-4} -alkoxy, and also represent benzyl or phenylethyl, each of which can optionally be substituted by the radicals indicated in the case of phenyl, and

R^3 to R^{10} have the meaning indicated above.

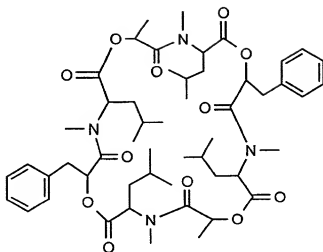
10 Particularly preferred compounds of the formula (I) are those in which

R^1 , R^2 , R^{11} and R^{12} independently of one another represent methyl, ethyl, propyl, isopropyl or n-, s-, t-butyl,

15 R^3 , R^5 , R^7 , R^9 represent hydrogen, straight-chain or branched C_{1-8} -alkyl, in particular methyl, ethyl, propyl, i-propyl, n-, s-, t-butyl, each of which can optionally be substituted by C_{1-4} -alkoxy, in particular methoxy, ethoxy, imidazolyl, indolyl or C_{1-4} -alkylthio, in particular methylthio, ethylthio, and
20 further represent phenyl, benzyl or phenethyl, each of which can optionally be substituted by halogen, in particular chlorine, and

R^4 , R^6 , R^8 , R^{10} independently of one another represent hydrogen, methyl, ethyl, n-propyl, n-butyl, vinyl, cyclohexyl, each of which can optionally be
25 substituted by methoxy, ethoxy, imidazolyl, indolyl, methylthio, ethylthio, and represent isopropyl, s-butyl and further represent optionally halogen-substituted phenyl, benzyl or phenylethyl.

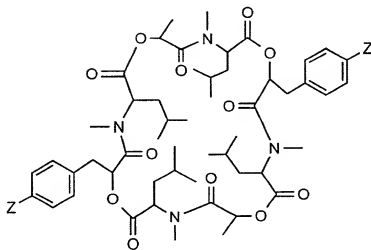
Furthermore, the compound PF 1022 of the following formula disclosed in EP-OS
30 (German Published Specification) 382 173 may be mentioned as a 24 ring-membered depsipeptide:



Moreover, the compounds disclosed in the PCT application WO 93/19053 may be mentioned as depsipeptides.

5

In particular, the compounds of the following formula may be mentioned from PCT application WO 93/19053:



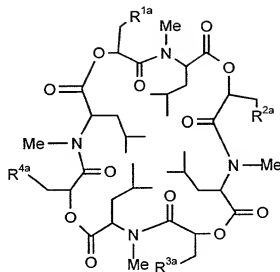
10

in which

Z represents morpholinyl, nitro, amino, mono- or dimethylamino, particularly emphatically morpholinyl.

15

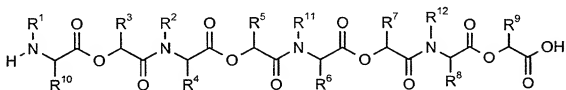
Moreover, compounds of the following formula may be mentioned:



in which

R^{1a} , R^{2a} , R^{3a} , R^{4a} independently of one another represent hydrogen, C_1 - C_{10} -alkyl or aryl, in particular phenyl, each of which is optionally substituted by hydroxyl, C_1 - C_{10} -alkoxy or halogen.

The compounds of the formula (I) can be prepared by cyclizing open-chain octadepsipeptides of the formula (II)



(II)

in which

R^1 to R^{12} have the meaning indicated above,

in the presence of a diluent and in the presence of a coupling reagent.

Suitable coupling reagents are all compounds which are suitable for the formation of an amide bond (cf., for example: Houben-Weyl, Methoden der organischen Chemie

[Methods of Organic Chemistry], Volume 15/2; Bodanszky et al., Peptide Synthesis 2nd ed. (Wiley / Sons, New York 1976).

5 The following reagents and methods are preferably suitable: active ester method using pentafluorophenol (Pfp), N-hydroxysuccinimide, 1-hydroxybenzotriazole, coupling using carbodiimides, such as dicyclohexylcarbodiimide or N'-(3-dimethylaminopropyl)-N-ethyl-carbodiimide (Ebc), and the mixed anhydride method or coupling using phosphonium reagents, such as benzotriazol-1-yl-oxy-tris(dimethylaminophosphonium) hexafluorophosphate (BOP), bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl), or using phosphonic acid ester reagents, such as diethyl cyanophosphonate (DEPC) and diphenylphospharyl azide (DPPA).

10 Coupling using bis(2-oxo-3-oxazolidinyl)-phosphonium acid chloride (BOP-Cl) and N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC) in the presence of 1-hydroxybenzotriazole (HOBt) is particularly preferred.

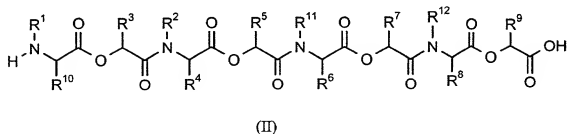
15 The reaction is carried out at temperatures from 0 – 150°C, preferably at 20 to 100°C, particularly preferably at room temperature.

20 Suitable diluents are all inert organic solvents. These include, in particular, aliphatic and aromatic, optionally halogenated hydrocarbons, such as pentane, hexane, heptane, cyclohexane, petroleum ether, benzine, ligroin, benzene, toluene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and o-dichlorobenzene, furthermore ethers such as diethyl and dibutyl ether, glycol dimethyl ether and diglycol dimethyl ether, tetrahydrofuran and dioxane, furthermore ketones, such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, moreover esters, such as methyl acetate and ethyl acetate, further-
25 more nitriles, e.g. acetonitrile and propionitrile, benzonitrile, glutaronitrile, moreover amides, e.g. dimethylformamide, dimethylacetamide and N-methylpyrrolidone, and
30 also dimethyl sulfoxide, tetramethylene sulfone and hexamethylphosphoramide.

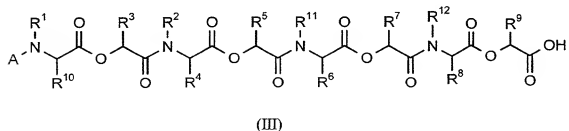
The compounds of the formulae (II) and the coupling reagents are employed in the ratio 1:1 to 1:1.5 to one another. An approximately equimolar ratio is preferred.

After the reaction has taken place, the diluent is distilled off and the compounds of the formula (I) are purified in a customary manner, e.g. by chromatography.

The open-chain octadepsipeptides of the formula (II)



in which the radicals have the meanings indicated above are obtained by hydrogenolyzing compounds of the formula (III)



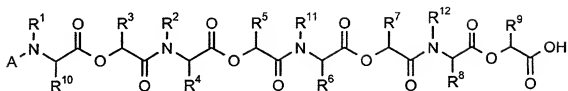
in which

A [lacuna] benzyl and

R¹ to R¹² have the meaning indicated above,

in the presence of a diluent and of a catalyst.

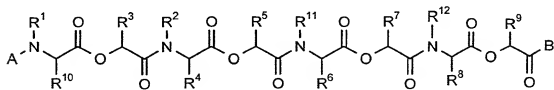
The compounds of the formula (III)



(III)

5 in which the radicals have the meaning indicated above, are obtained by

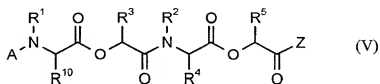
hydrolyzing compounds of the formula (IV)



(IV)

in which the radicals A and R¹ to R¹² have the meaning indicated above and B represents t-butoxy.

Compounds of the formula (IV) and their stereoisomers are obtained by condensing tetrapeptides of the formula (V)



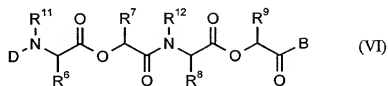
in which

A represents benzyl and

Z represents OH, and

R^1, R^2, R^3, R^4, R^5 and R^{10} have the meaning indicated above

and tetrapeptides of the formula (VI)



in which

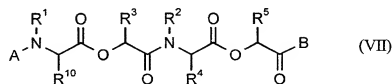
D represents hydrogen and

B represents tert-butoxy, and

R⁶, R⁷, R⁸, R⁹, R¹¹ and R¹² have the meaning indicated above,

in the presence of a diluent and of a coupling reagent.

Tetrapeptides of the formula (V) are obtained by saponifying tetrapeptides of the formula (VII)



in which

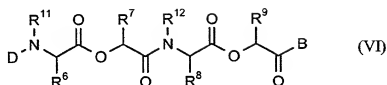
A represents benzyl and

B represents tert-butoxy, and

R¹, R², R³, R⁴, R⁵ and R¹⁰ have the meaning indicated above,

in the presence of a diluent and of a protonic acid.

Tetrapeptides of the formula (VI)

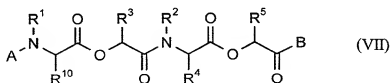


in which

D represents hydrogen and

B represents tert-butoxy and the other radicals have the meaning indicated above,

are obtained by hydrogenolyzing tetrapeptides of the formula (VII)



in which

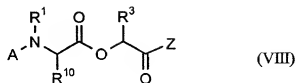
A represents benzyl and

B represents tert-butoxy, and

R¹, R², R³, R⁴, R⁵ and R¹⁰ have the meaning indicated above,

in the presence of a diluent and of a catalyst.

Tetrapeptides of the formula (VII) are obtained by condensing dipeptides of the formula (VIII)



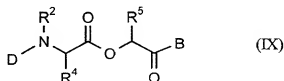
in which

A represents benzyl and

Z represents OH, and

R¹, R³ and R¹⁰ have the meaning indicated above and

dipeptides of the formula (IX)



in which

D represents hydrogen and

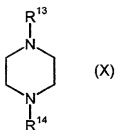
B represents tert-butoxy, and

R², R⁴ and R⁵ have the meaning indicated above,

in a diluent in the presence of a coupling reagent.

The depsipeptides disclosed in WO 93/19 053 or in EP-OS (German Published Specification) 382 173 can be contained by the methods described there.

The piperazines include all compounds of the formula (X)



in which

R^{13} and R^{14} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, and $-\text{CONR}^{15}\text{R}^{16}$ or $-\text{CSNR}^{15}\text{R}^{16}$, in which

R^{15} and R^{16} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted alkyl or cycloalkyl.

Preferred compounds of the formula (X) are those in which

R^{13} and R^{14} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, and $-\text{CONR}^{15}\text{R}^{16}$ or $-\text{CSNR}^{15}\text{R}^{16}$, in which

R^{15} and R^{16} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C_1 - C_6 -alkyl or C_3 - C_8 -cycloalkyl.

Particularly preferred compounds of the formula (X) are those in which

R^{13} and R^{14} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally

substituted C₁-C₄-alkyl, C₆-cycloalkyl, and -CONR¹⁵R¹⁶ or -CSNR¹⁵R¹⁶, in which

R¹⁵ and R¹⁶ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C₁-C₄-alkyl or C₆-cycloalkyl.

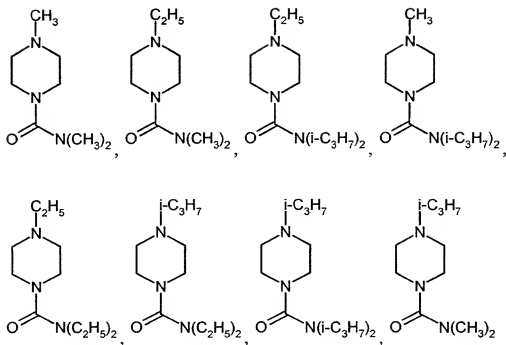
Very particularly preferred compounds of the formula (X) are those in which

10 R^{13} and R^{14} independently of one another represent identical or different substituents of the group hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl having 1 to 9 identical or different halogen atoms of the series F, Cl, or Br, C₆-cycloalkyl, and -CONR¹⁵R¹⁶ or -CSNR¹⁵R¹⁶, in which

R¹⁵ and R¹⁶ independently of one another represent identical or different substituents of the group hydrogen, C₁-C₄-alkyl or C₆-cycloalkyl.

20 The following compounds may be mentioned by way of example, but not restrictively:

25 piperazine, diethylcarbamazine, N,N'-dimethylpiperazine, N-methylpiperazine, N,N'-diethylpiperazine, N-ethylpiperazine, N-ethyl-N'-methylpiperazine, N,N'-dipropylpiperazine, N-propylpiperazine, N-ethyl-N'-propylpiperazine, N-methyl-N'-propylpiperazine, N-cyclohexylpiperazine, N,N'-dicyclohexylpiperazine,



- 5 piperazine and diethylcarbamazine may be especially emphasized here.

The piperazines are generally known organic compounds and are commercially obtainable or can be obtained by known methods. (Mehlhorn et al. Diagnostik und Therapie der Parasitosen des Menschen 2nd Edition, Gustav Fischer (1995),
 10 Mehlhorn et al. Diagnostik und Therapie der Parasitosen von Haus-, Nutz- und Heimtieren, 2nd Edition Gustav Fischer (1993)).

- The compositions according to the invention are suitable for controlling pathogenic endoparasites which occur in humans and in animal keeping and animal breeding in
 15 the case of agricultural animals, breeding animals, zoo animals, laboratory animals, experimental animals and pets and have favorable toxicity to warm-blooded animals. They are effective against all or individual stages of development of the pests and also against resistant and normally sensitive species. As a result of the control of the pathogenic endoparasites, disease, cases of death and yield reductions (e.g. in the
 20 production of meat, milk, wool, hides, eggs, honey etc.) should be reduced, so that more economical and simpler animal keeping is possible as a result of the use of the active compounds. The pathogenic endoparasites include cestodes, trematodes, nematodes, acantocephalae, in particular:

From the order of the Pseudophyllidea e.g.: *Diphyllobothrium* spp., *Spirometra* spp., *Schistocephalus* spp., *Ligula* spp., *Bothridium* spp., *Diphlogonoporus* spp.

From the order of the Cyclophyllidae e.g.: *Mesocestoides* spp., *Anoplocephala* spp., *Paranoplocephala* spp., *Moniezia* spp., *Thysanosomus* spp., *Thysaniezia* spp., *Avitellina* spp., *Stilesia* spp., *Cittotaenia* spp., *Andrya* spp., *Bertiella* spp., *Taenia* spp., *Echinococcus* spp., *Hydatigera* spp., *Davainea* spp., *Raillietina* spp., *Hymenolepis* spp., *Echinolepis* spp., *Echinocotyle* spp., *Diorchis* spp., *Dipylidium* spp., *Joyeuxiella* spp., *Diplopylidium* spp.

From the subclass of the Monogenea e.g.: *Gyrodactylus* spp., *Dactylogyrus* spp., *Polystoma* spp.

From the subclass of the Digenea e.g.: *Diplostomum* spp., *Posthodiplostomum* spp., *Schistosoma* spp., *Trichobilharzia* spp., *Ornithobilharzia* spp., *Austrobrilharzia* spp., *Gigantobilharzia* spp., *Leucochloridium* spp., *Brachylaima* spp., *Echinostoma* spp., *Echinoparyphium* spp., *Echinochasmus* spp., *Hypoderaeum* spp., *Fasciola* spp., *Fasciolides* spp., *Fasciolopsis* spp., *Cyclocoelum* spp., *Typhlocoelum* spp., *Paramphistomum* spp., *Calicophoron* spp., *Cotylophoron* spp., *Gigantocotyle* spp., *Fischoederius* spp., *Gastrothylacus* spp., *Notocotylus* spp., *Catantropis* spp., *Plagiorchis* spp., *Prosthogonimus* spp., *Dicrocoelium* spp., *Eurytrema* spp., *Troglo-trema* spp., *Paragonimus* spp., *Collyriclum* spp., *Nanophyetus* spp., *Opisthorchis* spp., *Clonorchis* spp., *Metorchis* spp., *Heterophyes* spp., *Metagonimus* spp.

From the order of the Enoplida e.g.: *Trichuris* spp., *Capillaria* spp., *Trichomosoides* spp., *Trichinella* spp.

From the order of Rhabditia e.g.: *Micronema* spp., *Strongyloides* spp.

From the order of Strongylida e.g.: *Stronylus* spp., *Triodontophorus* spp., *Oesophagodontus* spp., *Trichonema* spp., *Gyalocephalus* spp., *Cylindropharynx* spp., *Poteriostomum* spp., *Cyclococercus* spp., *Cylicostephanus* spp., *Oesophagostomum*

spp., Chabertia spp., Stephanurus spp., Ancylostoma spp., Uncinaria spp., Bunostomum spp.

- 5 Globocephalus spp., Syngamus spp., Cyathostomum spp., Metastrongylus spp., Dictyocaulus spp., Muellerius spp., Protostrongylus spp., Neostrongylus spp., Cystocaulus spp., Pneumostrongylus spp., Spicocaulus spp., Elaphostrongylus spp., Parelaphostrongylus spp., Crenosoma spp., Paracrenosoma spp., Angiostrongylus spp., Aelurostrongylus spp., Filaroides spp., Parafilaroides spp., Trichostrongylus spp., Haemonchus spp., Ostertagia spp., Marshallagia spp., Cooperia spp.,
- 10 Nematodirus spp., Hyostrongylus spp., Obeliscoides spp., Amidostomum spp., Ollulanus spp., Cylicocyclus spp., Crateostomum spp., Cylicodontophorus spp.

From the order of the Oxyurida e.g.: Oxyuris spp., Enterobius spp., Passalurus spp., Syphacia spp., Aspicularis spp., Heterakis spp.

- 15 From the order of the Ascaridia e.g.: Ascaris spp., Toxascaris spp., Toxocara spp., Parascaris spp., Anisakis spp., Ascaridia spp.

- 20 From the order of the Spirurida e.g.: Gnathostoma spp., Physaloptera spp., Thelazia spp., Gongylonema spp., Habronema spp., Parabronema spp., Draschia spp., Dracunculus spp.

- 25 From the order of the Filariida e.g.: Stephanofilaria spp., Parafilaria spp., Setaria spp., Loa spp., Dirofilaria spp., Litomosoides spp., Brugia spp., Wuchereria spp., Onchocerca spp.

From the order of the Gigantorhynchida e.g.: Filicollis spp., Moniliformis spp., Macracanthorhynchus spp., Prosthenechis spp.

- 30 The agricultural and breeding animals include mammals such as cattle, horses, sheep, pigs, goats, camels, water buffalo, donkeys, rabbits, fallow deer, reindeer, fur-bearing animals such as mink, chinchilla, racoon, birds such as chickens, geese, turkeys,

ducks ostriches, freshwater and saltwater fish such as trout, carps, eels, reptiles, insects such as honeybees and silkworms.

5 The laboratory and experimental animals include mice, rats, guinea-pigs, golden hamsters, dogs and cats.

The pets include dogs and cats.

10 Administration can be carried out both prophylactically and therapeutically.

15 The active compound mixtures are administered directly or enterally, parenterally, dermally, nasally in the form of suitable preparations, by treatment of the habitat or with the aid of active compound-containing molded articles such as strips, plates, tapes, collars, ear tags, limb bands, marking devices.

20 Enteral administration of the active compound mixtures is carried out, for example, orally in the form of powders, tablets, capsules, pastes, drinks, granules, orally administrable solutions, suspensions and emulsions, boli, medicated feed or drinking water. Dermal administration is carried out, for example, in the form of dipping, spraying or pouring-on and spotting-on. Parenteral administration is carried out, for example, in the form of injection (intramuscular, subcutaneous, intravenous, intraperitoneal) or by implants.

25 Suitable preparations are:

Solutions such as injection solutions, oral solutions, concentrates for oral administration after dilution, solutions for use on the skin or in body cavities, pour-on formulations, gels;

30 Emulsions and suspensions for oral or dermal administration and also for injection; semi-solid preparations;

Formulations in which the active compound mixture is processed in an ointment base or in an oil-in-water or water-in-oil emulsion base;

5 Solid preparations such as powders, premixes or concentrates, granules, pellets, tablets, boli, capsules; aerosols and inhalants, active compound mixture-containing molded articles.

10 Injection solutions are administered intravenously, intramuscularly and subcutaneously.

Injection solutions are prepared by dissolving the active compound mixture in a suitable solvent and adding possible additives such as solubilizers, acids, bases, buffer salts, antioxidants, preservatives. The solutions are sterile-filtered and bottled.

15 Solvents which may be mentioned are: physiologically tolerable solvents such as water, alcohols such as ethanol, butanol, benzyl alcohol, glycerol, propylene glycol, polyethylene glycols, N-methyl-pyrrolidone, and mixtures thereof.

20 The active compound mixture can optionally also be dissolved in physiologically tolerable vegetable or synthetic oils which are suitable for injection.

25 Solubilizers which may be mentioned are: solvents which promote the dissolution of the active compound mixture in the main solvent or prevent its precipitation. Examples are polyvinylpyrrolidone, polyoxyethylated castor oil, polyoxyethylated sorbitan ester.

Preservatives are: benzyl alcohol, trichlorobutanol, p-hydroxybenzoic acid ester, n-butanol.

30 Oral solutions are administered directly. Concentrates are administered orally after prior dilution to the administration concentration. Oral solutions and concentrates are

prepared as described above in the case of the injection solutions, it being possible to dispense with working under sterile conditions.

5 Solutions for use on the skin are applied drop by drop, smoothed on, rubbed in, splashed on or sprayed on. These solutions are prepared as described above in the case of the injection solutions.

10 It may be advantageous to add thickeners during the preparation. Thickeners are: inorganic thickeners such as bentonites, colloidal silicic acid, aluminum monostearate, organic thickeners such as cellulose derivatives, polyvinyl alcohols and their copolymers, acrylates and metacrylates.

15 Gels are applied to the skin or smoothed on or introduced into body cavities. Gels are prepared by mixing solutions which have been prepared as described in the case of the injection solutions with sufficient thickener that a clear material having an ointment-like consistency results. The thickeners employed are those indicated further above.

20 Pour-on formulations are poured onto or splashed onto restricted areas of the skin, the active compound penetrating the skin and acting systemically.

25 Pour-on formulations are prepared by dissolving, suspending or emulsifying the active compound mixture in suitable skin-compatible solvents or solvent mixtures. If appropriate, further auxiliaries, such as colorants, absorption-promoting substances, antioxidants, light screens, tackifiers are added.

30 Solvents which may be mentioned are: water, alkanols, glycols, polyethylene glycols, polypropylene glycols, glycerol, aromatic alcohols such as benzyl alcohol, phenyl-ethanol, phenoxyethanol, esters such as ethyl acetate, butyl acetate, benzyl benzoate, ethers such as alkylene glycol alkyl ethers such as dipropylene glycol monomethyl ether, diethylene glycol mono-butyl ether, ketones such as acetone, methyl ethyl ketone, aromatic and/or aliphatic hydrocarbons, vegetable or synthetic oils, DMF,

dimethylacetamide, N-methylpyrrolidone, 2,2-dimethyl-4-oxy-methylene-1,3-dioxolane.

5 Colorants are all colorants, which can be dissolved or suspended, permitted for use on animals.

Absorption-promoting substances are, for example, DMSO, spreading oils such as isopropyl myristate, dipropylene glycol pelargonate, silicone oils, fatty acid esters, triglycerides, fatty alcohols.

10 Antioxidants are sulfites or metabisulfites such as potassium metabisulfite, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, tocopherol.

Light screens are, for example, novantisolic acid.

15 Tackifiers are, for example, cellulose derivatives, starch derivatives, polyacrylates, natural polymers such as alginates, gelatin.

Emulsions can be administered orally, dermally or as injections.

20 Emulsions are either of the water-in-oil type or of the oil-in-water type.

They are prepared by dissolving the active compound mixture either in the hydrophobic or in the hydrophilic phase and homogenizing this with the solvent of
25 the other phase with the aid of suitable emulsifiers and, if appropriate, further auxiliaries such as colorants, absorption-promoting substances, preservatives, antioxidants, light screens, viscosity-increasing substances.

30 Hydrophobic phases (oils) which may be mentioned are: paraffin oils, silicone oils, natural vegetable oils such as sesame oil, almond oil, castor oil, synthetic triglycerides such as caprylic/capric biglyceride, triglyceride mixture with plant fatty acids of chain length C₈₋₁₂ or other specially selected natural fatty acids, partial

glyceride mixtures of saturated or unsaturated fatty acids which possibly also contain hydroxyl groups, mono- and diglycerides of the C₈/C₁₀ fatty acids.

5 Fatty acid esters such as ethyl stearate, di-n-butyl adipate, hexyl laurate, dipropylene glycol pelargonate, esters of a branched fatty acid of medium chain length with saturated fatty alcohols of chain length C₁₆-C₁₈, isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of chain length C₁₂-C₁₈, isopropyl stearate, oleyl oleate, decyl oleate, ethyl oleate, ethyl lactate, waxy fatty acid esters such as artificial duck uropygial gland fat, dibutyl
10 phthalate, diisopropyl adipate, ester mixtures related to the latter etc.

Fatty alcohols such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol, oleyl alcohol.

15 Fatty acids such as oleic acid and its mixtures.

Hydrophilic phases which may be mentioned are:

Water, alcohols such as propylene glycol, glycerol, sorbitol and their mixtures.

20 Emulsifiers which may be mentioned are: nonionic surfactants, e.g. polyoxyethylated castor oil, polyoxyethylenated sorbitan monooleate, sorbitan monostearate, glyceryl monostearate, polyoxyethyl stearate, alkylphenol polyglycol ether;

25 ampholytic surfactants such as di-Na N-lauryl-β-iminodipropionate or lecithin;

anionic surfactants, such as Na laurylsulfate, fatty alcohol ether sulfates, mono/dialkyl polyglycol ether orthophosphoric acid ester monoethanolamine salt;

30 cationic surfactants such as cetyltrimethylammonium chloride.

Further auxiliaries which may be mentioned are: substances which increase viscosity and stabilize the emulsion such as carboxymethylcellulose, methylcellulose and other cellulose and starch derivatives, polyacrylates, alginates, gelatin, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, copolymers of methyl vinyl ether and maleic anhydride, polyethylene glycols, waxes, colloidal silicic acid or mixtures of the substances mentioned.

Suspensions can be administered orally, dermally or as an injection. They are prepared by suspending the active compound in a carrier liquid, if appropriate with addition of further auxiliaries such as wetting agents, colorants, absorption-promoting substances, preservatives, antioxidants, light screens.

Carrier liquids which may be mentioned are all homogeneous solvents and solvent mixtures.

Wetting agents (dispersants) which may be mentioned are the surfactants indicated further above.

Further auxiliaries which may be mentioned are those indicated further above.

Semi-solid preparations can be administered orally or dermally. They differ from the suspensions and emulsions described above only by their higher viscosity.

For the production of solid preparations, the active compound is mixed with suitable carriers, if appropriate with addition of auxiliaries, and brought into the desired form.

Carriers which may be mentioned are all physiologically tolerable solid inert substances. Those which may be used are inorganic and organic substances. Inorganic substances are, for example, sodium chloride, carbonates such as calcium carbonate, hydrogencarbonates, aluminas, silicic acids, argillaceous earths, precipitated or colloidal silica, phosphates.

Organic substances are, for example, sugar, cellulose, foodstuffs and feedstuffs such as milk powder, animal meals, cereal meals and coarse cereal meals, starches.

5 Auxiliaries are preservatives, antioxidants and colorants which have already been mentioned further above.

10 Further suitable auxiliaries are lubricants and glidants such as magnesium stearate, stearic acid, talc, bentonites, disintegration-promoting substances such as starch or crosslinked polyvinylpyrrolidone, binders such as starch, gelatin or linear polyvinylpyrrolidone, and dry binders such as microcrystalline cellulose.

15 In the preparations, the active compound mixtures can also be present as a mixture with further synergists or with other active compounds which act against pathogenic endoparasites. Such active compounds are, for example, L-2,3,5,6-tetrahydro-6-phenyl-imidazothiazole, benzimidazole carbamates, pyrantel.

Ready-to-use preparations contain the active compound mixtures in concentrations of 10 ppm – 20% by weight, preferably of 0.1-10% by weight.

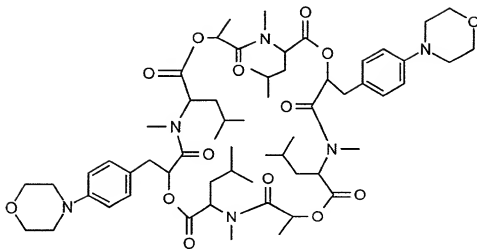
20 Preparations which are diluted before administration contain the active compound mixtures in concentrations of 0.5-90% by weight, preferably of 5 to 50 percent by weight.

25 In general, it has proven advantageous to administer amounts of the mixture according to the invention of approximately 10 to approximately 100 mg of active compound mixture per kg of body weight per day to achieve effective results. 10 to 50 mg of active compound mixture per kg of body weight are preferred.

30 In general, a weight ratio of piperazine to depsipeptide such as 50:1 to 1000:1, preferably 100:1 to 1000:1, very particularly preferably 250:1 to 1000:1, in particular 250:1 and 1000:1, is adhered to in the compositions.

10009930-10001

In the biological examples, the compound of the formula



disclosed in WO 93/19 053, was employed as "depsipeptide I".

5

The biological tests were carried out according to the known procedures (Plant et al. Pesticide Science, 1996, 48, p. 351 ff.).

Biological examples**Table 1**5 Synergistic effect of piperazine and depsipeptide I against *Trichinella spiralis* in vitro

	Concentration ($\mu\text{g/ml}$)	Action
Piperazine	1000	0-1
	500	0
Depsipeptide I	0.01	0-1
	0.001	0
Piperazine/depsipeptide I	1000/0.01	1-2
Piperazine/depsipeptide I	500/0.01	1-2

0 = no action; 1 = weak action; 2 = good action

10 **Table 2**

Synergistic effect of piperazine and depsipeptide I against mouse nematodes

Heterakis spumosa	Dose (mg/kg)	Action	Nematospir- ides dibius	Dose (mg/kg)	Action
Piperazine	4 x 250	1	Piperazine	2 x 2000	2
	4 x 100	0		4 x 1000	1
Depsipeptide I	4 x 1	1	PF1022-221	4 x 1	2
	4 x 0.5	1		4 x 0.5	0-2
Piperazine/ depsipeptide I	4 x 250/ 4 x 1	3	Piperazine/ PF1022-221	2 x 2000/ 4 x 1	2-3
Piperazine/ depsipeptide I	4 x 100/ 4 x 1	2	Piperazine/ PF1022-221	4 x 1000/ 4 x 1	2-3

0 = worm reduction <50 %; 1 = worm reduction 50-75 %; 2 = worm reduction 75-90 %; 3 = complete action, worm reduction >90 %

15

Preparation examples

Examples of the preparation of the cyclic depsipeptides having 24 ring atoms:

- 5 1. Preparation of the compounds of the formula (I).

10 BOP-Cl (0.124 mmol) was added at 0°C to a solution of the compound of the formula II (0.104 mmol) and Hünig's base (0.258 mmol) in dichloromethane (100 ml) and the mixture was stirred at room temperature for 24 h. After this time, the same amounts of BOP-Cl and base were added and the mixture was stirred for a further 24 h. The solution was washed twice with satd sodium hydrogencarbonate solution, dried over sodium sulfate and concentrated. The residue was purified by column chromatography using the eluent cyclohexane/ethyl acetate 2:1.

15 Compounds of the formula (I) were obtained in which the substituents have the following meaning (table 3):

Table 3

No.	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}	R ^{5a}	R ^{6a}	R ^{7a}	R ^{8a}	R ^{9a}	R ^{10a}	R ^{11a}	R ^{12a}	FAB-MS m/z (%)
1	Et	Et	Me	s-Bu	Bn	s-Bu	Me	s-Bu	Bn	s-Bu	Et	Et	
2	Propyl	Propyl	"	"	"	"	"	"	"	"	Propyl	Propyl	
3	i-Propyl	i-Propyl	"	"	"	"	"	"	"	"	i-Propyl	i-Propyl	
4	Me	Me	"	s-Bu	"	s-Bu	"	s-Bu	"	s-Bu	Me	Me	948 (82, (+H) ⁺)
5	Me	Me	"	i-Pr	"	i-Pr	"	i-Pr	"	i-Pr	Me	Me	915 (100, (M+Na) ⁺) 893 (55, (M+H) ⁺)
6	Me	Me	"	Bn	"	Bn	"	Bn	"	Bn	Me	Me	1107 (100, (M+Na) ⁺) 1085 (8, (M+H) ⁺)
7	Me	Me	"	s-Bu	2-Cl-Bn	s-Bu	"	s-Bu	2-Cl-Bn	s-Bu	Me	Me	
8	Me	Me	"	"	2-Cl-Bn	"	"	"	3-Cl-Bn	"	Me	Me	
9	Me	Me	"	"	4-Cl-Bn	"	"	"	4-Cl-Bn	"	Me	Me	
10	Propyl	i-Propyl	"	"	-Bn	"	"	"	-Bn	"	Propyl	i-Propyl	

Me = methyl

Et = ethyl

Bu = butyl

Pr = propyl

Bn = benzyl

Examples of the preparation of the compounds of the formula (II)

5

10

Table 4

No.	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}	R ^{5a}	R ^{6a}	R ^{7a}	R ^{8a}	R ^{9a}	R ^{10a}	R ^{11a}	R ^{12a}
11	Et	Et	Me	s-Bu	Bn	s-Bu	Me	s-Bu	Bn	s-Bu	Et	Et
12	Propyl	Propyl	"	"	"	"	"	"	"	"	Propyl	Propyl
13	i-Propyl	i-Propyl	"	"	"	"	"	"	"	"	i-Propyl	i-Propyl
14	Me	Me	"	"	"	"	"	"	"	"	Me	Me
15	Me	Me	"	i-Pr	"	i-Pr	"	i-Pr	"	i-Pr	Me	Me
16	Me	Me	"	Bn	"	Bn	"	Bn	"	Bu	Me	Me
17	Me	Me	"	s-Bu	2-Cl-Bn	s-Bu	"	s-Bu	2-Cl-Bn	s-Bu	Me	Me
18	Me	Me	"	"	3-Cl-Bn	"	"	"	3-Cl-Bn	"	Me	Me
19	Me	Me	"	"	4-Cl-Bn	"	"	"	4-Cl-Bn	"	Me	Me
20	Propyl	i-Propyl	"	"	-Bn	"	"	"	-Bn	"	Propyl	i-Propyl

Me = methyl

Et = ethyl

s-Bu = s-butyl

Bn = benzyl

Preparation of the compounds of the formula (III)

5 HCl gas was passed into a solution of the tert-butyl ester of the formula (IV) (1.609 mmol) in dichloromethane (40 ml) at 0°C for 1.5 h. The mixture was then warmed to room temperature and stirred for 12 h. The solution was concentrated in a rotary evaporator and dried in a high vacuum. The residue was reacted without further purification.

10 Analogously, compounds of the formula (III) were obtained in which the substituents have the following meaning (table 5):

10009930-110901

Table 5

No.	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}	R ^{5a}	R ^{6a}	R ^{7a}	R ^{8a}	R ^{9a}	R ^{10a}	R ^{11a}	R ^{12a}	A
21	Et	Et	Me	s-Bu	Bn	s-Bu	Me	s-Bu	Bn	s-Bu	Et	Et	Bn
22	Propyl	Propyl	"	"	"	"	"	"	"	"	Propyl	Propyl	"
23	i-Propyl	i-Propyl	"	"	"	"	"	"	"	"	i-Propyl	i-Propyl	"
24	Me	Me	"	"	"	"	"	"	"	"	Me	Me	"
25	Me	Me	"	i-Pr	"	i-Pr	"	i-Pr	"	i-Pr	Me	Me	"
26	M4	Me	"	Bn	"	Bn	"	Bn	"	Bn	Me	Me	"
27	Me	Me	"	s-Bu	2-Cl-Bn	s-Bu	"	s-Bu	2-Cl-Bn	s-Bu	Me	Me	"
28	Me	Me	"	"	2-Cl-Bn	"	"	"	3-Cl-Bn	"	Me	Me	"
29	Me	Me	"	"	4-Cl-Bn	"	"	"	4-Cl-Bn	"	Me	Me	"
30	Propyl	i-Propyl	"	"	-Bn	"	"	"	-Bn	"	Propyl	i-Propyl	"

Me = methyl

Et = ethyl

s-Bu = s-butyl

Bn = benzyl

Preparation of the compounds of the formula (IV)

A solution of ethyldiisopropylamine (0.912 mmol) and BOP-Cl (0.438 mmol) was added at 0°C to a solution of the tetradepsipeptides of the formula (VI) and (V) each (2.52 mmol) in dichloromethane (15 ml). The mixture was stirred at 0°C for 1 h and at room temperature for 1.5 h, diluted with 20 ml of dichloromethane, washed twice with a little water, dried over Na₂SO₄ and concentrated. The residue was purified on silica gel using the eluent cyclohexane/t-BuOMe = 2:1.

Preparation of the compounds of the formula (V)

HCl gas was passed at 0°C for 2 h into a solution of the tetradepsipeptide having the formula (VII) (2.848 mmol) in dichloromethane (50 ml).

The mixture was then stirred at room temperature for 8 h, concentrated and dried in a high vacuum. The residue was employed without further purification.

Preparation of the compounds of the formula (VI)

A solution of the tetradepsipeptide having the formula (VII) (9.53 mmol) in ethanol (37 ml) was treated with Pd(OH)₂/C (20%) (0.6 g) and hydrogenated at room temperature and normal pressure for about 3 h. The reaction mixture was filtered, concentrated and the residue was separated on silica gel using the eluent t-BuOMe/cyclohexane/ethanol = 1:1:0.5.

Preparation of the compounds of the formula (VII)

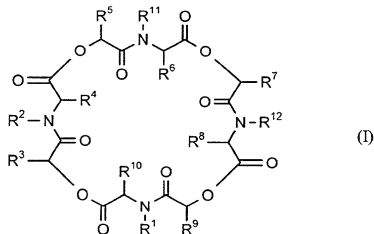
A solution of the dipeptide IX (22.9 mmol) and of the dipeptide VIIIa (27.5 mmol) in dichloromethane (80 ml) cooled to 0°C was treated with diisopropylethylamine (57.3 mmol) and BOP-Cl (29.8 mmol), stirred at 0°C for 1 h and at room temperature for 1 h. After filtering off the precipitate, the solution was diluted with dichloromethane, washed three times with a little water, dried over

sodium sulfate and concentrated. The residue was separated on silica gel using the eluent cyclohexane/ethyl acetate = 15:1.

10009930-110901

Patent claims

1. The use of piperazines for increasing the endoparasitocidal action of cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms.
2. An endoparasitocidal composition which contains piperazines together with cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms.
3. The use of piperazines together with cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms for the production of endoparasitocidal compositions.
4. The use of piperazines as claimed in claim 1, characterized in that the cyclic depsipeptides correspond to the formula (I)



in which

R^1 , R^2 , R^{11} and R^{12} independently of one another represent C_{1-8} -alkyl, C_{1-8} -halogenoalkyl, C_{3-6} -cycloalkyl, aralkyl, aryl,

R^3, R^5, R^7, R^9 independently of one another represents hydrogen or straight-chain or branched C_{1-8} -alkyl, which can optionally be substituted by

hydroxyl, C_{1-4} -alkoxy, carboxyl, $\begin{array}{c} \text{O} \\ \parallel \\ (-\text{COH}) \end{array}$, carboxamide, $\begin{array}{c} \text{O} \\ \parallel \\ (-\text{O}-\text{C}-\text{NH}_2) \end{array}$, imidazolyl, indolyl,

guanidino, -SH or C_{1-4} -alkylthio and further represents aryl or aralkyl which can be substituted by halogen, hydroxyl, C_{1-4} -alkyl, C_{1-4} -alkoxy,

R^4, R^6, R^8, R^{10} independently of one another represent hydrogen, straight-chain C_{1-5} -alkyl, C_{2-6} -alkenyl, C_{3-7} -cycloalkyl, each of which can optionally be substituted by hydroxyl, C_{1-4} -alkoxy, carboxyl, carboxamide, imidazolyl, indolyl, guanidino, SH or C_{1-4} -alkylthio, and represent aryl or aralkyl which can be substituted by halogen, hydroxyl, C_{1-4} -alkyl, C_{1-4} -alkoxy,

and their optical isomers and racemates.

5. The use as claimed in claim 4, characterized in that the cyclic depsipeptides correspond to the formula (I), in which

R^1, R^2, R^{11} and R^{12} independently of one another represent methyl, ethyl, propyl, isopropyl, n-, s-, t-butyl or phenyl, which is optionally substituted by halogen, C_{1-4} -alkyl, OH, C_{1-4} -alkoxy, and also represent benzyl or phenethyl, each of which can optionally be substituted by the radicals indicated in the case of phenyl, and

R^3 to R^{10} have the meaning indicated in claim 4.

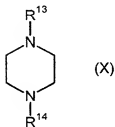
6. The use as claimed in claim 4, characterized in that the cyclic depsipeptides correspond to the formula (I), in which

R^1 , R^2 , R^{11} and R^{12} independently of one another represent methyl, ethyl, propyl, isopropyl or n-, s-, t-butyl,

R^3 , R^5 , R^7 , R^9 represent hydrogen, straight-chain or branched C_{1-8} -alkyl, in particular methyl, ethyl, propyl, i-propyl, n-, s-, t-butyl, each of which can optionally be substituted by C_{1-4} -alkoxy, in particular methoxy, ethoxy, imidazolyl, indolyl or C_{1-4} -alkylthio, in particular methylthio, ethylthio, and further represent phenyl, benzyl or phenethyl, each of which can optionally be substituted by halogen, in particular chlorine, and

R^4 , R^6 , R^8 , R^{10} independently of one another represent hydrogen, methyl, ethyl, n-propyl, n-butyl, vinyl, cyclohexyl, each of which can optionally be substituted by methoxy, ethoxy, imidazolyl, indolyl, methylthio, ethylthio, and represent isopropyl, s-butyl and further represent optionally halogen-substituted phenyl, benzyl or phenylethyl.

7. The use as claimed in claims 1 or 4 to 6, characterized in that the piperazines correspond to the formula (X),



in which

R¹³ and R¹⁴ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, and -CONR¹⁵R¹⁶ or -CSNR¹⁵R¹⁶, in which

R¹⁵ and R¹⁶ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted alkyl or cycloalkyl.

8. The use as claimed in claims 1 or 4 to 6, characterized in that the piperazines correspond to the formula (X), in which

R¹³ and R¹⁴ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C₁-C₆-alkyl, C₃-C₈-cycloalkyl, and -CONR¹⁵R¹⁶ or -CSNR¹⁵R¹⁶, in which

R¹⁵ and R¹⁶ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C₁-C₆-alkyl or C₃-C₈-cycloalkyl.

9. The use as claimed in claims 1 or 4 to 6, characterized in that the piperazines correspond to the formula (X), in which

R^{13} and R^{14} independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C_1 - C_4 -alkyl, C_6 -cycloalkyl, and $-CONR^{15}R^{16}$ or $-CSNR^{15}R^{16}$ in which

R¹⁵ and R¹⁶ independently of one another represent identical or different substituents of the group hydrogen, in each case optionally substituted C₁-C₄-alkyl or C₆-cycloalkyl.

10. The composition as claimed in claim 2, characterized in that the cyclic depsipeptides correspond to one of the definitions mentioned in claims 4 to 6 and/or the piperazines correspond to one of the definitions mentioned in claims 7 to 9.

10009930-110901

Endoparasiticial compositions

A b s t r a c t

The present invention relates to the use of piperazines for increasing the endoparasiticial action of cyclic depsipeptides, consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms, in endoparasiticial compositions, such compositions and the use of piperazines and cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring units and having 24 ring atoms for the production of endoparasiticial compositions.

10009930-110901

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought

on the invention entitled

"ENDOPARASITICIDAL SYNERGISTIC COMBINATION CONTAINING CYCLIC DEPSIPTIDES AND PIPERAZINES"

the specification of which is attached hereto,

or was filed on May 4, 2000

as a PCT Application Serial No. PCT/EP00/04014

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

199 21 887.0
(Number)

Germany
(Country)

May 12, 1999
(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)

(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)

(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1069-1080

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and this application and to transact all business in the Patent and Trademark Office

JOSEPH C. GIL, Patent Office Registration Number 26,602 ARON PREIS, Patent Office Registration Number 29,426
LYNDANNE M. WHALEN, Patent Office Registration Number 29,457 THOMAS W. ROY,
Patent Office Registration Number 29,582 RICHARD E. L. HENDERSON, Patent Office Registration Number 31,619
GODFRIED R. AKORLI, Patent Office Registration Number 28,779 N. DENISE BROWN, Patent Office
Registration Number 36,097 NOLAND J. CHEUNG, Patent Office Registration Number 39,138
DIDERICO VAN EYL, Patent Office Registration Number 38,641 CAROLYN M. SLOANE, Patent Office
Registration Number 44,339 JAMES R. FRANKS, Patent Office Registration Number 42,552
JACKIE ANN ZURCHER, Patent Office Registration Number 42,251
RAYMOND J. HARMUTH, Patent Office Registration Number 33,896

all of Bayer Corporation, Pittsburgh, Pennsylvania 15205-9741

Send Correspondence To: Direct Telephone Calls To:
Patent Department
Bayer Corporation (412) 777-2349
100 Bayer Road
Pittsburgh, Pennsylvania 15205-9741

FULL NAME OF SOLE OR FIRST INVENTOR Achim Harder		INVENTOR'S SIGNATURE <i>Achim Harder</i>	DATE 04.09.01
RESIDENCE D 51109 Köln, Germany DEX		CITIZENSHIP German	
POST OFFICE ADDRESS c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany			
FULL NAME OF SECOND INVENTOR Georg von Samson-Himmelstjerna		INVENTOR'S SIGNATURE <i>Georg von Samson-Himmelstjerna</i>	DATE 02.08.01
RESIDENCE D 42657 Solingen, Germany DEX		CITIZENSHIP German	
POST OFFICE ADDRESS Neuenkamper Str. 21, D 42657 Solingen, Germany			
FULL NAME OF THIRD INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF FOURTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF FIFTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF SIXTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF SEVENTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			